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(54) **Non-invasive mixing**

(57) The simultaneous mixing of the contents in each of a plurality of containers each including a liquid, is effected by simultaneously causing the containers each to be rotated about its own axis first in one direction and then in another. In an embodiment, the containers (42) are test-tubes mounted in a turntable (18) with a disc-shaped drive member (56) frictionally engaging each tube and rotatable (independently of turntable) in one direction and then the other, to cause each tube (42) to be rotated about its own axis to mix the contents therein. The turntable assembly is particularly suitable for use with automatic analysis machines.

FIG. 1

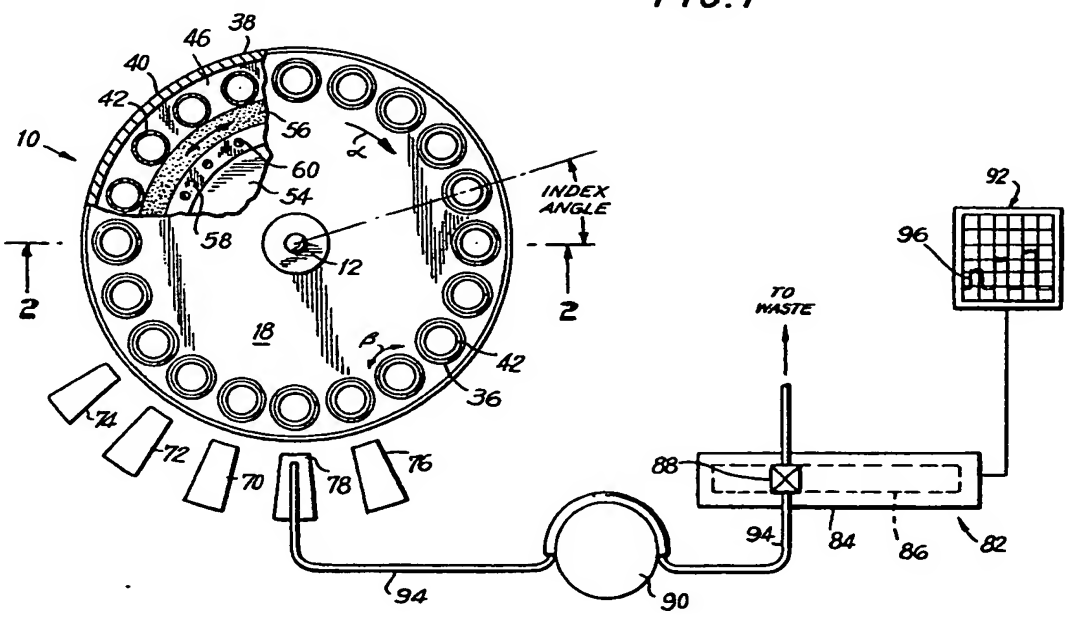

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FIG. 1

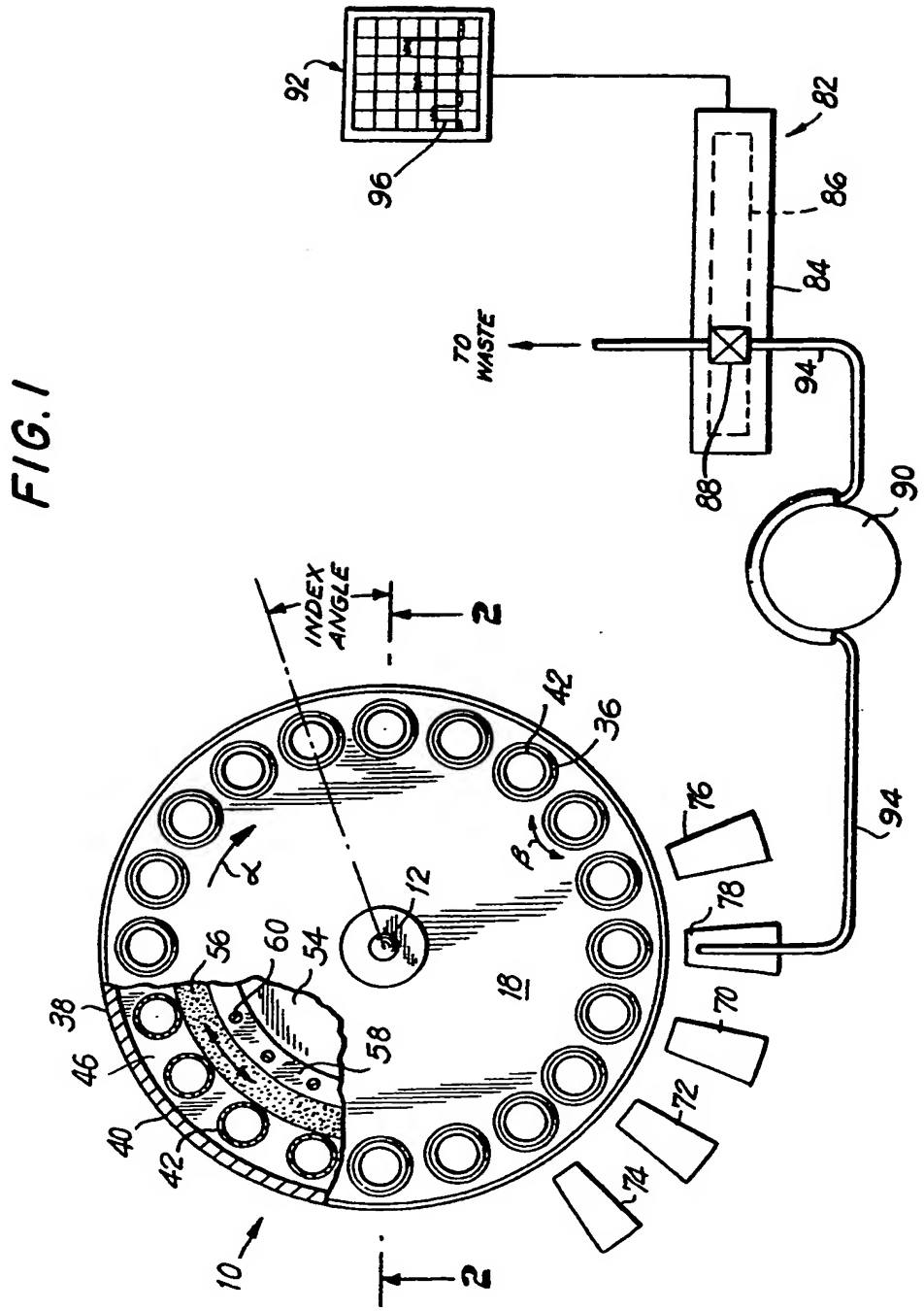


FIG. 2

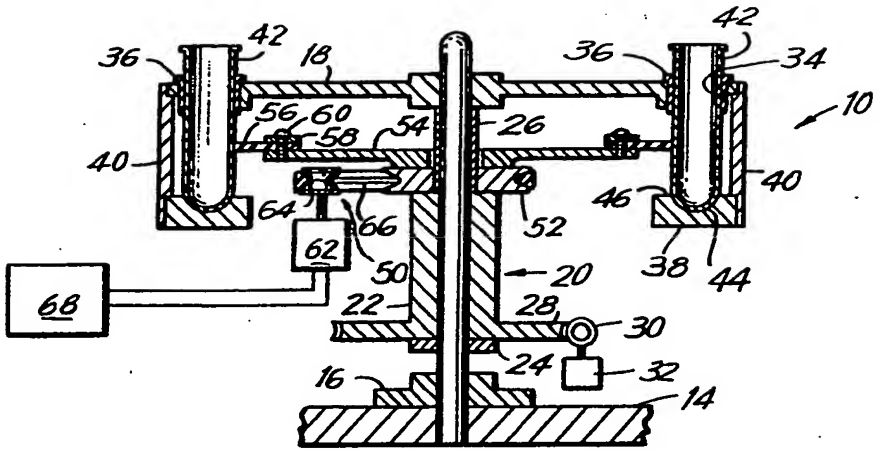
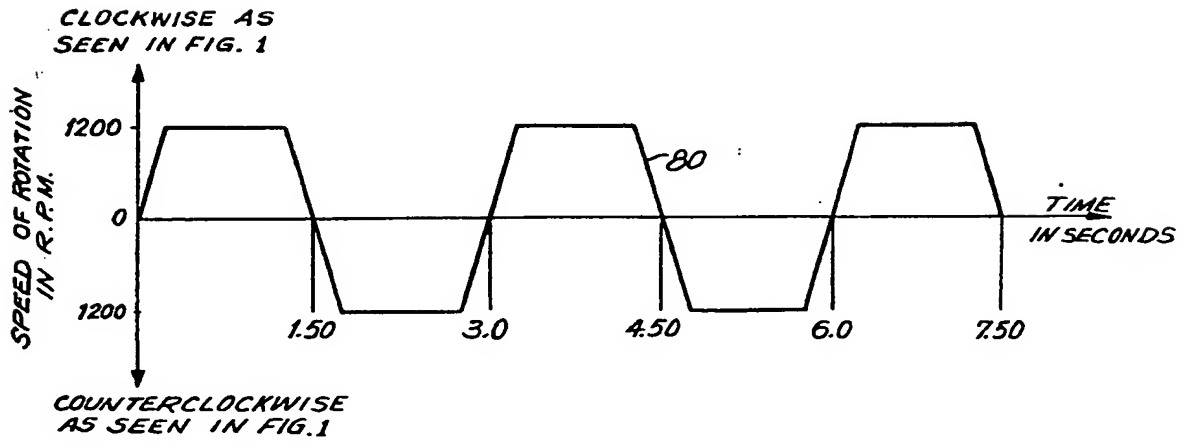


FIG. 3



SPECIFICATION

Non-invasive mixing method and apparatus

This invention relates to an apparatus and method for the concurrent, controlled, non-invasive mixing of a plurality of substances in individual containers, and more particularly (but not exclusively) for the automated mixing of substances for the operation of automated analytical devices.

A wide variety of mixing apparatus and methods are known in the prior art which operate invasively, e.g. through immersion of mechanical means, such as paddles or stirrers, into the substances to be mixed. Such prior art mixing apparatus and methods are less than satisfactory for use, for example, in present-day automated sample analysis devices (especially for immunological analyses) or systems employing particulate reagents. More specifically, such invasive mixing means can operate to: (a) cause cross-contamination between samples by introducing the residue from a preceding sample which remains on the mixing means into a succeeding sample; (b) cause dilution of the samples by introducing the residue of any wash liquid remaining on the mixing means following the "washing" thereof, as described in Eduard B. M. deJong, U.S. Patent 3,134,263; and/or (c) disrupt the relatively delicate chemical reaction by mechanical interference with the same, hence, adversely affecting the accuracy of the analysis results. In addition, and since certain automated analytical devices require the continuous mixing of a plurality of sample/reagent combinations contained in individual open containers supported on an indexible turntable, the operative utilization of a plurality of invasive mixing means, would be impractical.

Further, and although a variety of non-invasive mixing apparatus and methods are known in the prior art to effect mixing of substances by inducing one or more motions of the container, none are to our knowledge particularly suitable for utilization with automated analytical devices. For example, the paint mixing apparatus and method as disclosed in U.S. Patent 3,542,344 are limited in operation to closed containers which must be manually disposed on and removed from the mixing apparatus and, hence, unsuitable for use in the continuous and concurrent mixing of a plurality of open, independent sample containers supported upon an indexed turntable. In like manner, the specimen treatment apparatus disclosed in U.S. Patent 4,007,011, although relevant to an indexible turntable supporting a plurality of independent sample containers, is operable to oscillate said turntable, and thus said containers only intermittently, e.g. at the termination of each indexing operation. The resulting mixing effect is less than satisfactory for use in automated analytical devices employing particulate reagents, as intended by the present invention in one application thereof. Also, the liquid inspection method disclosed in U.S. Patent 3,528,544 comprises the use of an indexible turntable upon which a plurality of closed ampoules are rotatively disposed and rotated discontinuously and on a selected group basis by a plurality of belt drive means in different directions and at different speeds. Again, the discontinuity in rotation, coupled with the complexities of the plurality of belt drive means and the structure for holding and supporting the ampoules, render such apparatus less than satisfactory for use in an automated analysis apparatus of the nature discussed hereinabove.

We have now devised an apparatus and method for the controlled, non-invasive mixing of particulate substances in continuous fashion with a liquid medium, which are particularly suited for use in conjunction with automated analytical devices which require the continuous concurrent mixing of one or more particulate substances or reagents in a liquid medium at controlled mixing rates.

According to the invention, there is provided apparatus for the controlled, non-invasive mixing of substances disposed in a plurality of individual containers, comprising: rotatable means for supporting said containers for rotation relative thereto, container rotating means operable to concurrently rotate said plurality of containers about respective container axes in a first direction at a first predetermined speed and for a first predetermined time interval and, alternately, to concurrently rotate said same plurality of containers about respective container axes in a second direction opposite to said first direction at a second predetermined speed and for a second predetermined interval of time whereby, in use, mixing of said substances in said containers in continuously changing directions is effected.

In one preferred arrangement, there is provided apparatus for the controlled, non-invasive mixing of substances, comprising: a support shaft, a generally circular turntable supported for rotation on said support shaft, turntable indexing means supported for rotation on said support shaft and drivingly connected to said turntable, means to intermittently rotate said turntable indexing means to index said turntable, a plurality of generally cylindrical and equally sized containers arranged in a generally circular array on said turntable generally concentrically thereof, each of said containers being supported for rotation about its own axis on said turntable with the lower portion of the container extending below said turntable, a generally circular container drive disc supported for rotation on said support shaft below said turntable and generally concentrically thereof with the periphery of said drive disc extending into driving surface contact with the outer wall of each of said containers below said turntable, means to alternately rotate said container drive disc in opposite directions about said support shaft to in turn concurrently rotate said containers in opposite, alternating directions about respective container axes, said container drive disc rotating means being operable during both the indexing and dwell periods of said turntable whereby continuous mixing in continuously changing directions of substances in said containers is effected.

The invention also provides a method for the controlled, non-invasive mixing of substances which are disposed in a plurality of containers supported for rotation about respective container axes on rotatable

supporting means, which method comprises the steps of alternating between concurrent driven rotation by container drive means of said containers in one direction about respective container axes at a first predetermined speed and for a first predetermined time interval, and concurrent driven rotation by the same container drive means of said same containers in the opposite direction about respective container axes at a second predetermined speed and for a second predetermined time interval, whereby mixing of said substances in said containers in continuously changing directions is effected.

Preferably in the method and apparatus of the invention, said rotatable supporting means comprise an indexible turntable, said container rotating means being operable to rotate said containers both during the indexing and dwell periods of said turntable whereby, in use, the mixing of said substances in said containers in continuously changing directions is continuous during turntable operations.

The apparatus and method of the invention can be arranged to provide for the continuous mixing of substances contained in a plurality of open-topped, generally cylindrical containers arranged in a generally circular array on an indexible circular turntable. In such cases, each of the containers is supported on the turntable for rotation about its respective axis. The turntable forms part of a sample of automated analytical apparatus which is operable to quantitatively analyze samples reacted within the individual containers, e.g. by particle-agglutination techniques, as hereafter described. To effect mixing, a drive disc can be arranged to frictionally contact each of the containers and be driven continuously and in alternating opposite directions, i.e. clockwise and counterclockwise, to rotate each of the containers concurrently and in alternating opposite directions about their respective axes at a predetermined rotational speed and for a predetermined time period. Container rotation reversals are continuous, even during turntable indexing, to accelerate completion of the reaction with attendant maximization of the accuracy of the analysis results. Such mixing technique finds particular application where particulate reagents are used, such as to perform particle-agglutination immunoassays. It has been observed that such mixing very substantially increases the probability of contact of the particular reagents, so as to accelerate completion of the reaction.

In order that the invention may be more fully understood, reference is made to the accompanying drawings, wherein:

Figure 1 is a top plan view of one embodiment of apparatus of the invention (by way of example only), and includes parts cut away, and the generally schematic depiction of sample and reagent intake and off-take means, and of sample analysis means, all for purposes of completeness of illustration and description;

Figure 2 is a cross-sectional view taken generally along line 2-2 in Figure 1 and includes the generally schematic depiction of the drive motor means; and

Figure 3 is a graph illustrating reaction tube rotational velocity versus time.

Referring now to Figures 1 and 2 which illustrate a preferred embodiment of the invention, an indexible sampler assembly is indicated generally at 10, and comprises a central shaft 12 supported in non-rotatable manner from a fixed support platform 14 and a fixed support base 16.

An indexible circular turntable is indicated at 18 and is rotatable intermittently relative to shaft 12 by indexing drive means, generally indicated at 20. The indexing means 20 comprise a drive hub 22 supported for rotation relative to shaft 12 by a thrust bearing, as indicated at 24. A drive sleeve 26 is rotatably disposed on shaft 12, the respective upper and lower extremities being fixedly connected to the top of drive hub 22 and the underside of turntable 18. A helical gear 28 is defined on the periphery of drive hub 22 which meshes with a driving worm gear indicated at 30 which is in turn driven by a stepping motor 32. Under these circumstances, periodic energization of stepping motor 32 will in turn result in intermittent rotation, or indexing of turntable 18 about support shaft 12, as indicated by arrow α (alpha) in Fig. 1.

A generally circular array of reaction tube mounting apertures 34 is formed, as shown, in turntable 18 adjacent the periphery thereof, and a generally cylindrical, lipped bearing 36 of appropriate low-friction material, for example, nylon, is disposed in each aperture.

A ring-shaped support tray 38 is carried, as shown from turntable 18 by circumferentially spaced support members 40. Preferably, support tray 38 is secured to the support members 40 in readily detachable manner for convenient disassembly of sampler 10.

Each reaction tube 42 is disposed in a bearing 36 for rotation in both a clockwise and counterclockwise direction, as indicated by the arrow β (beta) in Fig. 1, about its axis, the bottom of the tube resting in a shaped depression 44 formed in the upper surface 46 of support tray 38. Preferably, the support tray 38 is fabricated from a low-friction material, for example, nylon, to minimize friction and the attendant possibility of unwanted reaction tube heating. Alternatively, cup-shaped bearings, not shown, could be inserted in depressions 44 for low-friction support as described of the reaction tubes 42 in each instance.

Means operable in accordance with the teachings of the invention for effecting the precisely controlled, bi-directional rotation of the reaction tubes 42 are indicated generally at 50, and comprise a driven pulley 52 and a connected drive hub 54 which are mounted as shown for rotation as a unit around drive sleeve 26. Pulley 52 rests on the upper surface of the drive hub 22 with complete freedom for relative rotation therebetween.

An annularly shaped drive disc 56 is affixed, as shown to hub 54 by an attachment ring 58 and spaced fastening means 60. The drive disc 56 is fabricated of suitably rigid material of high surface friction characteristics, for example, silicone rubber. As illustrated in Figs. 1 and 2, the periphery of drive disc 56 firmly contacts the side walls of each of reaction tubes 42, such that rotation of drive disc 56 in the clockwise direction, as seen in Fig. 1, will result in concomitant driven rotation of all the reaction tubes

42 about the respective axes thereof at the same rotational velocity in the counterclockwise direction. Also, rotation of the drive disc 56 in the counterclockwise direction, as seen in Fig. 1, will result in concomitant driven rotation of all the reaction tubes 42 in the clockwise direction. Due to the significantly greater diameter of the drive disc 56, the speeds of rotation of the reaction tubes 42 will, in all instances, be substantially greater than the rotational speed of the drive disc, so as to achieve thorough mixing of substances in the reaction tubes, as described in greater detail hereinbelow, without the necessity for potentially cumbersome high speed rotation of the driven pulley 52, the drive hub 54 and the drive disc 56.

Although not shown, with the exception of thrust bearing 24, it will be readily understood by those skilled in this art that appropriate bearings may be provided as and where needed with regard to all of the relatively rotatable components of sampler assembly 10.

A reversible, variable speed electric drive motor 62 is operable to rotate drive pulley 64. A drive belt 66 connects drive pulley 64 to driven pulley 52 for driven rotation of the latter attendant energization of drive motor 62. As a result, energization of drive motor 62 to drive, in turn, driven pulley 52, drive hub 54 and drive disc 56, respectively concurrently rotates each of the reaction tubes 42, as described, about their respective axes. The substantial difference in the respective diameters of pulleys 64 and 66 allows drive motor 68 to be operated at more efficient, higher torque speeds without attendant overspeeding of the drive disc 56 or reaction tubes 42. The drives motor torque amplification factor resulting from the difference in pulley diameters permits extremely rapid decelerations and accelerations of drive disc 56 and, hence, of reaction tubes 42 between the oppositely directed rotational velocities, as discussed in greater detail hereinbelow.

Drive motor control means indicated schematically at 68 in Fig. 2 are operable to adjustably and precisely control the rotational speed, direction of rotation, and time of rotation in each direction of drive motor 62. As a result, the rotational speeds, directions of rotation, and times of rotation in each direction of the respective reaction tubes 42 may be precisely controlled by operation of the control means 68 throughout a wide range by appropriate adjustment of the latter.

For example, the sampler assembly 10 finds useful application in automated systems for performing a particle-agglutination counting immunoassays. In such systems, a plurality of blood serum samples are quantitatively analyzed with regard to the free thyroxin levels thereof, which are indicative of the thyroid hormone levels of the respective blood serum sample donors. Such analysis may be termed a "one particle" methodology, in that an appropriately diluted blood serum sample of precisely predetermined, relatively small volume is contained in each of the reaction tubes 42. Each such sample volume is thoroughly mixed with a predetermined volume of a particulate reagent comprising an appropriate antibody-coated agglutination medium, for example, latex beads of approximately one micron diameter, and coated with a rabbit anit-thyroxin antibody to the blood serum sample constituent of interest and, also, a predetermined volume of an appropriate, likewise specific antigen or tracer, for example, a non-particulate soluble polymeric material such as dextran, which acts as a specific bonding agent tending to form crosslinkages between the specific antibody-coated latex beads. Accordingly, an optically detectable agglutination of the reagent results which is in inverse proportion to the serum free thyroxin level in the blood serum sample of interest. This is to say, the serum free thyroxin competes with the antigen for bonding to the antibody-coated latex beads whereupon, the greater the concentration of the thyroxin, the smaller the overall level of latex bead agglutination.

To maximize the accuracy of the analysis results, the particulate reagent or latex beads should be bonded together by the specific antibody-antigen crosslinkages to the maximum extent commensurate with the blood serum sample thyroxin level. Accordingly, the latex beads, which are of approximately one micron in diameter and, hence, do not inherently move rapidly by diffusion must be driven into intimate contact in the reaction mixture. In addition, since the latex bead concentration in the reaction mixture is relatively low, there are relatively large distances between the latex beads and the rate per unit of time of natural contact therebetween is very small. Thus, for example, if a typical reaction mixture is allowed to stand unmixed, the time for the agglutination reaction to proceed to a representative steady state or equilibrium condition can be as long as 4 hours. If, on the other hand, this same solution is constantly mixed by agitation to induce collisions between the latex beads, such time is reduced to under 30 minutes. This mixing, however, must be gentle enough so that the latex beads, once agglutinated, are not again separated by the mixing action, while nonetheless strong enough to achieve steady state or equilibrium in the shortest practical time period. Thus will be clear that substantial care must be taken in determining the nature and rate of mixing.

Referring again in detail to Figs. 1 and 2, a blood serum sample intake probe, and antibody-coated latex bead (particulate reagent), antigen (tracer) and buffer dispensing probes, and, also, a reacted sample solution off-take probe are schematically indicated at 70, 72, 74, 76 and 78, respectively, and are operatively disposed relative to the sampler means 10. The dispensing probes 70, 72, 74 and 76 are operable to non-invasively, sequentially dispense carefully predetermined volumes of the indicated substances into each of the reaction tubes 42, and the off-take probe 78 is operable to withdraw or aspirate predetermined volume of the reaction mixture from the reaction tubes for subsequent analysis.

Automated, sample solution analysis means are indicated generally at 82, and comprise an optical housing 84 containing an optical detecting system as schematically indicated in dashed lines at 86, and which in turn includes a flow cell as schematically

indicated at 88. A reacted sample solution pump is indicated at 90, and a conduit 94 extends as shown from the reacted sample solution off-take probe 78 through pump 90 to flow cell 88, whereby predetermined volumes of the reacted sample solutions may be supplied in turn from the respective reaction tubes 42 by the off-take probe 78 and pump 90 for flow to and through flow cell 88 as indicated with attendant automated optical analyses thereof by the optical system 86. Sample solution analysis results recording means are indicated generally at 92 and may, for example, take the depicted form of a strip chart recorder which is operable to sequentially record the results of the respective sample solution analyses in graphical form as indicated, for example, by curve 96.

In operation, the bi-directional rotation means 50 is energized to concomitantly rotate all reaction tubes 42, as described hereinabove, at a predetermined speed in clockwise and counterclockwise directions during controlled successive time intervals. Also, indexing means 20 is energized to periodically advance turntable 18 in the clockwise direction, as indicated. As each rotating reaction tube 42 is indexed, in turn, in respect of sample intake probe 70, antibody-coated latex bead probe 72, and antigen probe 74, carefully predetermined volumes of those substances are, in turn, non-invasively dispensed into the same. The rotation of each reaction tube 44 provides for the thorough, albeit non-destructive, mixing of such substances, so as to promote the agglutination reaction. More specifically, as reaction tube rotation in one direction reaches its predetermined speed, a vortex is created in the reaction tube with attendant mixing thereof. As the direction of tube rotation is abruptly reversed, however, this vortex is collapsed by the frictional forces exerted on such mixture by the inner tube wall of the reaction tube, which is now rapidly accelerating in the opposite direction, which tends to and ultimately reforms the vortex by rotation of the reaction mixture in the other direction. Thus, each reversal in the rotational direction of the reaction tubes 42 generates tearing forces within the reaction mixture, which, while sufficient to effect thorough mixing and promote the agglutination reaction, are insufficient to tear apart those latex beads which have already agglutinated. The speed of rotation of the reaction tubes 42 is, in any event, carefully predetermined in each instance to be below that speed of rotation at which the respective sample solutions would be spilled therefrom by the described mixing action.

Subsequent indexing of the turnable 18 advances each reaction tube 42, in turn, with continuous sample solution mixing, as described, relative to the buffer dispensing probe 72 (for the addition of buffer thereto to insure the generation of a standard curve by the optical detecting system 86) and subsequently relative to the off-take probe 78, whereupon a predetermined volume of the thoroughly mixed reaction mixture is withdrawn for feed to the optical detecting system 86, which is operative to determine the extent of latex bead agglutination and, hence, the serum free thyroxin level in the blood serum sample. Recording of the results of this determination for each of the blood serum samples of interest is effected by analysis results recording means 92.

Of particular significance is the fact that the reaction mixture contained in each reaction tube 42 is continuously mixed, even during indexing or turntable 18, from the time the various constituents thereof are introduced into the reaction tube until a volume thereof is withdrawn, as described, for optical analysis. As a result, the agglutination reaction is continuously promoted, without interruption, to accelerate the reaction and achieve steady state or equilibrium within a minimum time period.

A representative, although by no means limitative, graph of the rotational velocity and direction of a reaction tube 42 versus time is indicated at 80 in Fig. 3. Such graph makes clear that drive motor control means 68 can be adjusted to provide a reversal in rotational direction of the reaction tubes 42 every approximately 1.5 seconds and a peak rotational velocity in each direction of approximately 1200 revolutions per minute. In addition, representative dwell time, i.e., time between the introduction of the antibody-coated latex beads (particulate reagent) and the antigen (tracer) to commence the agglutination reaction and the subsequent withdrawal of a volume of the reached mixture for optical analysis, may be approximately 15 minutes.

Although disclosed in detail hereinabove as applied to the mixing of biological samples attendant the operation of an automated analytical device, it will be obvious to those skilled in this art that the teachings of this invention are by no means limited to such application.

Various changes may, of course, be made in the herein disclosed preferred embodiment of this invention without departing from the spirit and scope thereof as defined in the appended claims.

CLAIMS

1. Apparatus for the controlled, non-invasive mixing of substances disposed in a plurality of individual containers, comprising: rotatable means for supporting said containers for rotation relative thereto, container rotating means operable to concurrently rotate said plurality of containers about respective container axes in a first direction at a first predetermined speed and for a first predetermined time interval and, alternately, to concurrently rotate said same plurality of containers about respective containers axes in a second direction opposite to said first direction at a second predetermined speed and for a second predetermined interval of time whereby, in use, mixing of said substances in said containers in continuously changing directions is effected.

2. Apparatus according to claim 1, wherein said rotatable supporting means comprise an indexible turntable, said container rotating means being operable to rotate said containers both during the indexing and dwell periods of said turntable whereby, in use, the mixing of said substances in said containers in continuously changing directions is continuous during turntable operations.

3. Apparatus according to claim 2, wherein said containers are arranged in a generally circular array

on said turntable, and said container rotating means include means for drivingly engaging each of said plurality of containers.

4. Apparatus according to claim 3, wherein said containers are generally cylindrical and of generally equal outer diameters, said container rotating means comprise a generally circular drive disc which is in surface contact with the outer walls of each of said containers and which is disposed generally concentrically of said container array whereby, driven rotation of said drive disc in one direction results in concomitant driven rotation of said containers about respective container axes in the opposite direction.

5. Apparatus according to claims 2, 3 or 4, further comprising adjustable speed drive means for driving said container rotating means, whereby the speed of rotation of said containers may be adjusted.

6. Apparatus according to claims 2, 3, 4 or 5, wherein said turntable is planar, said containers have respective rotational axes which are parallel and respectively substantially perpendicular to the plane of said turntable.

7. Apparatus according to any of claims 2 to 6, further comprising dispensing probe means operatively associated with said turntable and operable to sequentially non-invasively dispense predetermined quantities of said substances into said containers as the latter are indexed in turn into respective positions relative to said dispensing probe means by said turntable.

8. Apparatus according to any of claims 2 to 7, further comprising off-take probe means operatively associated with said turntable and operable to sequentially withdraw predetermined quantities of said substances from said containers as the latter are indexed in turn into respective positions relative to said off-take probe means by said turntable at the completion of substance mixing in each instance.

9. Apparatus according to claim 8, further comprising mixed substance analysis means operatively connected to said off-take probe whereby, said predetermined substance quantities may be sequentially supplied from said off-take probe to said analysis means for analysis in turn by the latter.

10. Apparatus according to any of claims 1 to 9, wherein said containers are open-topped.

11. Apparatus according to claim 10, wherein said first and second predetermined speeds of rotation are, in each instance, predetermined to be below that speed of container rotation at which said substances would be spilled from an open-topped container by substance mixing.

12. Apparatus according to any of claims 1 to 11, wherein said first and second speeds of rotation are substantially equal.

13. Apparatus according to any of claims 1 to 12, wherein said first and second time intervals are substantially equal.

14. Apparatus for the controlled, non-invasive mixing of substances, comprising: a support shaft, a generally circular turntable supported for rotation on said support shaft, turntable indexing means supported for rotation on said support shaft and drivingly connected to said turntable, means to intermittently rotate said turntable indexing means to index said turntable, a plurality of generally cylindrical and equally sized containers arranged in a generally circular array on said turntable generally concentrically thereof, each of said containers being supported for rotation about its own axis on said turntable with the lower portion of the container extending below said turntable, a generally circular container drive disc supported for rotation on said support shaft below said turntable and generally concentrically thereof with the periphery of said drive disc extending into driving surface contact with the outer wall of each of said containers below said turntable, means to alternately rotate said container drive disc in opposite directions about said support shaft to in turn concurrently rotate said containers in opposite, alternating directions about respective container axes, said container drive disc rotating means being operable during both the indexing and dwell periods of said turntable whereby continuous mixing in continuously changing directions of substances in said containers is effected.

15. Apparatus for the controlled, non-invasive mixing of substances disposed in a plurality of individual containers substantially as herein described with reference to Figures 1 and 2 of the accompanying drawings.

16. A continuous flow automated analyzer which includes apparatus as claimed in any preceding claim.

17. A method for the controlled, non-invasive mixing of substances which are disposed in a plurality of containers supported for rotation about respective container axes on rotatable supporting means, which method comprises the steps of alternating between concurrent driven rotation by container drive means of said containers in one direction about respective container axes at a first predetermined speed and for a first predetermined time interval, and concurrent driven rotation by the same container drive means of said same containers in the opposite direction about respective container axes at a second predetermined speed and for a second predetermined time interval, whereby mixing of said substances in said containers in continuously changing directions is effected.

18. A method according to claim 17, wherein said rotatable supporting means comprise an indexible turntable, and wherein the driven rotation of said containers comprises the further steps of continuing the driven rotation of said containers during both the indexing the dwell period of said turntable whereby the mixing of said substances in said containers in continuously changing directions is continuous during turntable operation.

19. A method according to claim 18, wherein said turntable is generally circular, said plurality of containers are arranged in a generally circular array on said turntable and generally concentric thereof, and wherein the driven rotation of said containers comprises the further steps of concomitantly drivingly engaging said plurality of containers for rotation of the same in said first and second directions.

20. A method according to claim 18 or 19, wherein alternation between respective directions of

container rotation is effected every approximately 1.5 seconds, and wherein the predetermined speed of rotation of said containers in each of said directions is approximately 1200 revolutions per minute.

21. A method according to claim 18, 19 or 20, further comprising the steps of sequentially non-invasively dispensing predetermined quantities of said substances into said containers as the latter are indexed in turn into appropriate positions by said turntable.

22. A method according to claim 18, 19, 20 or 21, further comprising the steps of sequentially withdrawing predetermined quantities of said substances from said containers as the latter are indexed in turn into appropriate positions by said turntable at the completion of substance mixing in each instance.

23. A method according to claim 22, further comprising the steps of sequentially supplying said withdrawn, mixed substance quantities to analysis means for analysis of said mixed substances.

24. A method according to any of claims 17 to 23, wherein said first and second speeds of rotation are substantially equal.

25. A method according to any of claims 17 to 24, wherein said first and second time intervals are substantially equal.

26. A method according to any of claims 17 to 25, wherein said containers are open-topped, and wherein said first and second speeds of rotation are, in each instance, predetermined to be below that speed of container rotation at which said substances would be spilled from an open-topped container by substance mixing.

27. A method according to claim 17 substantially as herein described with reference to Figures 1, 2 and 3 of the accompanying drawings.

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